original reports

Busulfan Plus Cyclophosphamide Versus Total Body Irradiation Plus Cyclophosphamide for Adults Acute B Lymphoblastic Leukemia: An Open-Label, Multicenter, Phase III Trial

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abstract

PURPOSE It remains controversial whether busulfan-based versus total body irradiation (TBI)–based regimens have comparable outcomes in patients with acute lymphoblastic leukemia (ALL) undergoing allogeneic hematopoietic stem-cell transplantation (allo-HSCT). We investigated the efficacy and toxicity of busulfan plus cyclophosphamide (BuCy) and TBI plus cyclophosphamide (TBI-Cy) conditioning in allo-HSCT for adult standard-risk B-cell-ALL in first complete remission (CR1).

PATIENTS AND METHODS We performed an open-label, randomized phase III trial at 13 hospitals in China. Eligible patients (age 14-65 years) had standard-risk ALL in CR1. Patients were randomly assigned (1:1) to BuCy (0.8 mg/kg four times per day on days –7 to –4 and cyclophosphamide 60 mg/kg once daily on days –3 to –2) or TBI-Cy (4.5 Gy TBI on days –5 to –4 and cyclophosphamide 60 mg/kg once daily on days –3 to –2). The primary end point was 2-year overall survival. Analysis was per protocol. This trial is registered with ClinicalTrials.gov (identifier: NCT02670252) and is complete.

RESULTS Between January 2016 and February 2020, 275 patients were assigned to receive BuCy (273 assessed) and 275 to TBI-Cy (272 assessed). The 2-year overall survival was 76.6% (95% CI, 71.7 to 81.8) and 79.4% (74.7 to 84.4; $P = .457$; difference 2.9%; 95% CI, –4.1 to 9.8; $P = .022$), indicating noninferiority of BuCy. The 2-year relapse was 20.2% (95% CI, 15.6 to 25.1) and 18.4% (14.0 to 23.2; $P = .616$), and the nonrelapse mortality was 11.0% (95% CI, 7.6 to 15.0) and 11.0% (7.7 to 15.1; $P = .988$) in the BuCy and TBI-Cy groups, respectively. There were no differences in regimen-related toxicity, graft-versus-host disease, or late effects between the two groups.

CONCLUSION The BuCy regimen has noninferior efficiency and safety as TBI-Cy (4.5 Gy × 2) for patients with adult standard-risk B cell-ALL in CR1 undergoing HLA-matched allo-HSCT.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is a curative therapy for patients with acute lymphoblastic leukemia (ALL).[1,2] Although there is still debate about the role of allo-HSCT in patients with standard-risk ALL in first complete remission (CR1), especially for adolescents and young adults, allo-HSCT is recommended for these populations according to various guidelines.[1-3] Traditionally, total body irradiation (TBI)–based regimens are considered the standard conditioning in patients with leukemia, especially in lymphoid malignancies.[4] However, TBI-based regimens are associated with serious lifelong adverse events (AEs), including interstitial pneumonia, cataracts, endocrine disturbances, and secondary malignancies.[5] Over the past few decades, intravenous busulfan (Bu) is introduced as the conditioning for allo-HSCT. Retrospective and perspective studies of myeloid malignancies reveal that Bu-based regimens gave noninferior or even superior survival.[6-8] In ALL, the studies comparing Bu-based and TBI-based regimens are mainly limited to retrospective studies, and the outcomes remain controversial.[9-13] A recent early-terminating randomized controlled trial (RCT) of pediatric ALL showed that chemotherapy conditioning, including Bu-based regimens, was associated

CONTEXT

Key Objective

Total body irradiation (TBI)–based myeloablative conditioning regimens are widely used in fit adults allografted for acute lymphoblastic leukemia (ALL). The role of busulfan (Bu)-based myeloablative regimes in this clinical setting remains a matter of conjecture. In this randomized trial, we compared the efficacy and safety of Bu plus cyclophosphamide (BuCy) and TBI-Cy conditioning regimens for adult B-cell-ALL with a standard-risk cytogenetic profile allografted using an HLA-matched donor.

Knowledge Generated

The BuCy regimen demonstrated noninferior survival, relapse, and disease-free survival compared with the TBI-Cy (4.5 Gy × 2) regimen and comparable safety profile.

Relevance *(C.F. Craddock)*

This study identifies a BuCy regimen as an alternative conditioning in adults allografted for ALL using a HLA-matched allogeneic-hematopoietic stem-cell transplantation.*

*Relevance section written by *JCO* Associate Editor Charles F. Craddock, MD.

with worse survival and higher relapse than TBI-based regimens.[14] To date, RCT of adult ALL is lacking as for comparison between Bu plus cyclophosphamide (BuCy) versus TBI plus cyclophosphamide (TBI-Cy). Herein, we performed an RCT to investigate the efficacy and safety of BuCy and TBI-Cy regimens for patients with adult B-cell ALL (B-ALL) with standard-risk cytogenetics in CR1 undergoing HLA-matched hematopoietic stem-cell transplantation (HSCT).

PATIENTS AND METHODS

Study Design and Participants

This study was an open-label, randomized, phase III trial (ClinicalTrials.gov identifier: NCT02670252) performed in 13 hospitals in China (Protocol, online only). Patients were eligible if they were age 14-65 years, had a diagnosis of B-ALL with standard-risk cytogenetics, achieved CR1, were willing to undergo HLA-matched HSCT (related or unrelated), and had an Eastern Cooperative Oncology Group performance status < 3. The diagnosis of B-ALL was based on the criteria from the National Comprehensive Cancer Network and categorized as standard-risk ALL on the basis of cytogenetics.[15] Patients were excluded if they had acute biphenotypic leukemia; uncontrolled infections or severe cardiovascular, pulmonary, hepatic, renal, or psychiatric disorders; or a history of other tumor within 2 years. The study protocol was approved by the ethics committee review board at each hospital, and written informed consent was obtained from each patient according to the Declaration of Helsinki before the initiation of the study.

Random Assignment and Masking

Patients were randomly assigned (1:1) to the BuCy or TBI-Cy regimen before transplantation. Random assignment was performed by permuted blocks (block size four) using a dedicated web-based random assignment system (Interactive Response Technology, Signant Health, Wayne, PA), which was independent of the study site staff and investigators. Treatment allocations were not masked to the investigators or the participants. Each patient was assigned a unique number. Data analysis and outcome evaluation were conducted in a masked manner.

Procedure

Two induction and consolidation chemotherapies were administered, including pediatric-inspired regimens (PDT-ALL-2016; Appendix Table A1 [online only])[16] and adult regimens[17] (Appendix Table A2, online only).

After enrollment, patients assigned to the BuCy group received intravenous Bu (0.8 mg/kg four times per day on days –7 to –4) with cyclophosphamide (60 mg/kg once daily on days –3 to –2). The TBI-Cy group was given TBI 4.5 Gy/d on days –5 and –4 from a linear accelerator with lung and lens shielding combined with intravenous cyclophosphamide (60 mg/kg once daily on days –3 to –2).

All patients received peripheral blood stem-cell grafts from an HLA-matched sibling donor (MSD) or matched unrelated donor (MUD). MSD (10/10 matching HLA-A, B, C, DR, and DQ loci) was the first choice for allo-HSCT. If MSD was unavailable, patients with a suitably MUD (10/10 matching) were eligible for MUD transplants. Methotrexate, cyclosporine A, and mycophenolate were used for graft-versus-host disease (GVHD) prophylaxis in MSD recipients.[18] Methotrexate, cyclosporine A, mycophenolate, and antithymocyte globulin (rabbit antihuman thymocyte immunoglobulin, Imtix Sangstat, Lyon, France) were used in MUD recipients.[18]

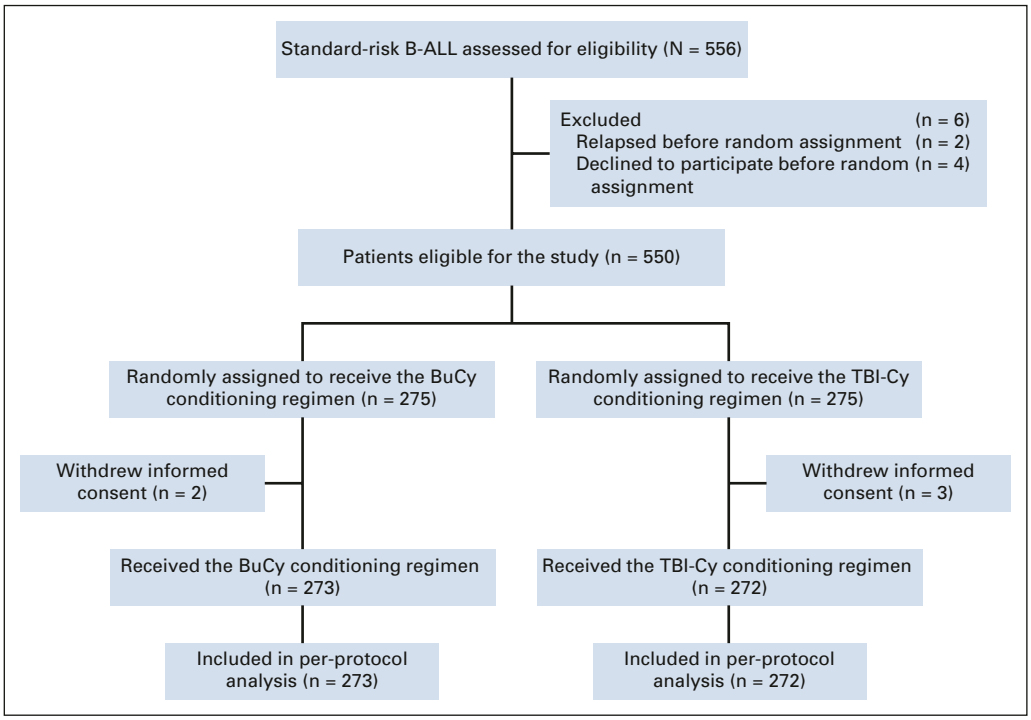

FIG 1. CONSORT diagram. B-ALL, B-cell acute lymphoblastic leukemia; BuCy, busulfan plus cyclophosphamide; TBI-Cy, total body irradiation plus cyclophosphamide.

Complete remission was defined as $< 5\%$ bone marrow (BM) blasts by morphologic evaluation with no evidence of extramedullary disease. Minimal residual disease (MRD) in BM was assessed by 8-flow cytometry before allo-HSCT, and cutoff values of MRD positivity (MRD^+) were defined as 0.01%.[19]

After enrollment, patients were followed up until this study was completed. BM assessments, physical examinations, and laboratory tests were assessed before random assignment, every month for the first 3 months post-transplantation, every 2 months from the fourth to ninth months, and then every 3 months until the study was completed.

Outcomes

The primary end point was 2-year overall survival (OS). The secondary end points included regimen-related toxicity (RRT), nonrelapse mortality (NRM), relapse, disease-free survival (DFS), AEs, and late effects. OS referred to the time from random assignment until death from any cause. NRM referred to death without relapse. Relapse was defined as either the reappearance of blasts in the blood or $> 5\%$ leukemic blasts in BM or evidence of extramedullary disease. DFS was defined as the time from random assignment until disease relapse or death from any cause. Neutrophil engraftment was defined as the first of 2 consecutive days taken to achieve an absolute neutrophil count of $\geq 0.5 \times 10^9$/L in the peripheral blood without growth factor support. Platelet engraftment was defined as the first of 3 consecutive days to maintain an untransmuted platelet count of $\geq 20 \times 10^9$/L. The achievement of full hemopoietic donor chimerism was defined as more than 95% of cells being of donor origin. RRT was graded according to Bearman's criteria.[20] AEs were recorded within 100 days post-transplantation according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.3. Late effects were according to the published recommendation.[21] Late effects were recorded 6 months post-transplantation and graded by Common Terminology Criteria for Adverse Events 4.0.3. Acute GVHD (aGVHD) and chronic GVHD (cGVHD) were graded according to published guidelines[22,23] and were categorized as AEs according to our report.[18] cGVHD was excluded as a late effect in this study.

Statistical Analysis

The sample size was calculated on the basis of the primary end point, 2-year OS, which was approximately 70% in the TBI-Cy group.[24] The design was a noninferiority study with a 10% margin, and a minimum of 520 patients (260 in each group) were required to provide the study with a one-sided α of .05 and a power of 80%. After adjusting for 5% dropout, the total sample size was 546 patients (273 in each group). Sample size calculation was performed using PASS software (version 11.0). To show noninferiority, the upper limit of the 95% CI for the difference in 2-year OS between the two groups

TABLE 1. Patient Demographics and Baseline Characteristics

Item	BuCy	TBI-Cy
No. of patients	273	272
Patient age, years, median (range)	26 (14-59)	27 (14-61)
Sex, No. (%)		
Female/male	115 (42.1)/158 (57.9)	97 (35.7)/175 (64.3)
Initial WBC, No. (%)		
≥ 30/< 30 (10^9/L)	97 (35.5)/176 (64.5)	81 (29.8)/191 (70.2)
Chemotherapy regimen, No. (%)		
Pediatric-type/adult-type	79 (28.9)/194 (71.1)	97 (35.7)/175 (64.3)
Cycles required to achieve CR, No. (%)		
≥ 2/1	42 (15.4)/231 (84.6)	52 (19.1)/220 (80.9)
MRD status after induction, No. (%)		
Positive *v* negative	98 (35.9)/175 (64.1)	89 (32.7)/183 (67.3)
MRD status at HSCT, No. (%)		
Positive *v* negative	48 (17.6)/225 (82.4)	39 (14.3)/233 (85.7)
Donor, No. (%)		
MUD/MSD	68 (24.9)/205 (75.1)	76 (27.9)/196 (72.1)
Donor age, years, median (range)	32 (10-55)	31 (13-57)
Donor-recipient sex match, No. (%)		
Male/female	72 (26.4)	56 (20.6)
Female/female	43 (15.8)	41 (15.1)
Male/male	95 (34.8)	114 (41.9)
Female/male	63 (23.1)	61 (22.4)
CMV IgG status, No. (%)		
D–/R–	21 (7.7)	17 (6.3)
D+/R–	10 (3.7)	6 (2.2)
D–/R+	13 (4.8)	8 (2.9)
D+/R+	229 (83.9)	241 (88.6)
Median infused CD34+ cells (range)	8.4 (4.2-13.0)	9.0 (4.3-13.4)

Abbreviations: BuCy, busulfan plus cyclophosphamide; CMV, cytomegalovirus; CR, complete remission; D, donor; HSCT, hematopoietic stem-cell transplantation; IgG, immunoglobulin G; MRD, minimal residual disease; MSD, matched sibling donor; MUD, matched unrelated donor; R, recipient; TBI-Cy, total body irradiation plus cyclophosphamide.

(TBI-Cy group minus BuCy group) could not exceed 10%. The hypothesis test for survival rates was conducted on the basis of Kaplan-Meier estimation and Greenwood's formula. OS and DFS were estimated using the Kaplan-Meier methodology and compared using the log-rank test. Cumulative incidences of neutrophil and platelet engraftment, aGVHD, cGVHD, relapse, and NRM were estimated accounting for competing events and compared using Gray's test. Competing events are defined as follows: for GVHD and engraftments, death without the event; for relapse, death without relapse; and for NRM, relapse. The categorical variables and continuous variables were analyzed by using the chi-square and Mann-Whitney U tests.

For multivariable analyses, Cox regression was used to explore the impact of risk factors for time-to-event variables on OS and DFS. Competing risks regression was used for relapse and NRM. Competing events are defined as follows: for relapse, death without relapse and for NRM, relapse. The following variables were included in the univariable analysis: patient sex, patient age, initial WBC, chemotherapy regimen, courses required to achieve CR1, MRD status, donors, conditioning regimens, aGVHD, and cGVHD. GVHD was evaluated from occurrence of GVHD as a time-dependent variable. Variables with $P < .10$ in univariate analysis or variables known to influence the outcome were included in the multivariable analysis. The corresponding hazard ratio and 95% CI were estimated using the Cox proportional hazards model and the cause-specific hazard model.[25]

The analysis was per protocol on February 20, 2022. Intervals were calculated from the day of random assignment until the last day of follow-up, transplant-related death, or relapse.

All statistical tests were based on a two-tailed hypothesis with a significance level of .05 except for the inferiority hypothesis. SPSS 22 (SPSS Inc, Chicago, IL) and R version 3.3.0 (R Development Core Team, Vienna, Austria) were used for data analysis. The trial is registered at ClinicalTrials.gov (identifier: NCT02670252) and is completed.

RESULTS

Study Population

From January 2016 to February 2020, 550 eligible patients were enrolled from 13 centers and randomly assigned to receive BuCy (n = 275) or TBI-Cy (n = 275). Five patients withdrew consent (Fig 1). The allocated treatment was delivered to 273 and 272 in the BuCy and TBI-Cy groups, respectively. Patient baseline was balanced between groups (Table 1).

Engraftment

All patients achieved hematopoietic reconstitution except one patient who died of intracranial hemorrhage in the BuCy group. The median time to neutrophil engraftment was 12 (range 9-41) days and 12 (9-38) days in the BuCy and TBI-Cy groups ($P = .384$), respectively. The

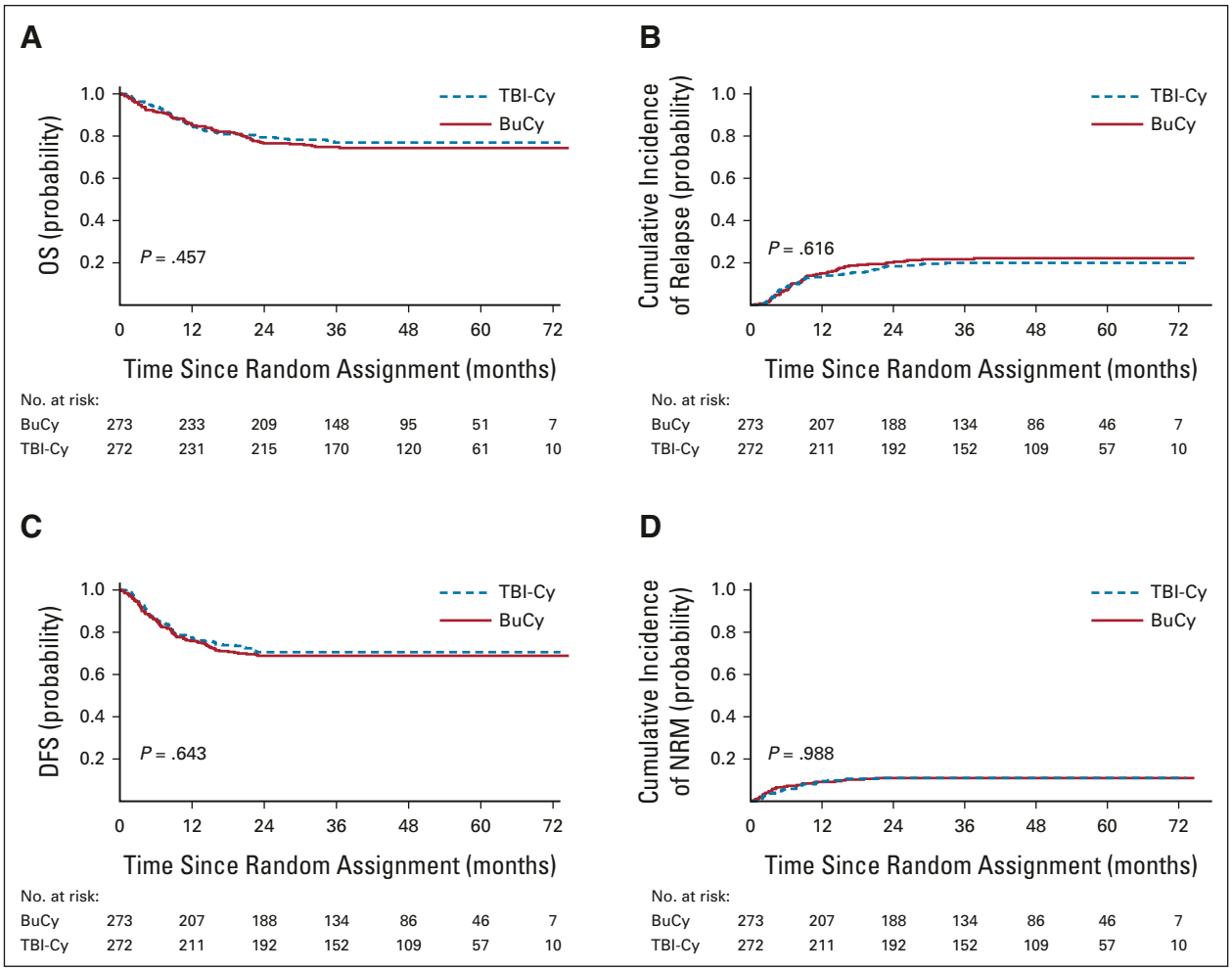

FIG 2. Outcomes of allogeneic-hematopoietic stem-cell transplantation with BuCy or TBI-Cy conditioning regimens: (A) survival by conditioning regimens, (B) cumulative incidence of disease relapse by conditioning regimens, (C) DFS by conditioning regimens, and (D) cumulative incidence of NRM by conditioning regimens. BuCy, busulfan plus cyclophosphamide; DFS, disease-free survival; NRM, nonrelapse mortality; OS, overall survival; TBI-Cy, total body irradiation plus cyclophosphamide.

corresponding median time to platelet engraftment was 14 days (range 9-125 days) and 13 days (9-107 days; $P = .632$). The cumulative incidences of neutrophil engraftment at day 30 were 99.2% (95% CI, 95.9 to 99.5) and 98.5% (95% CI, 96.5 to 99.9) in the BuCy and TBI-Cy groups, respectively ($P = .258$); the corresponding incidences for platelet engraftment were 87.9% (95% CI, 83.3 to 91.2) and 92.3% (95% CI, 88.0 to 94.8; $P = .166$). All patients achieved complete donor chimerism by day 60 post-transplantation.

Overall Survival

With a median follow-up of 42 months, 414 patients survived and 131 died, including 69 in the BuCy group and 62 in the TBI-Cy group. The causes of death were similar in the two groups (Appendix Table A3, online only). The 2-year OS was 76.6% (95% CI, 71.7 to 81.8) and 79.4% (95% CI, 74.7 to 84.4) in the BuCy and TBI-Cy groups, respectively ($P = .457$; Fig 2A). The treatment-adjusted difference was 2.9% (95% CI, –4.1 to 9.8; $P = .022$). Because the upper bound of the 95% CI (9.8) did not exceed 10%, noninferiority was shown.

Post hoc multivariable analysis of risk factors for OS showed that MRD^+ at transplantation, aGVHD, and cGVHD were risk factors for OS, whereas pediatric-type chemotherapy had better OS (Table 2). An exploratory post hoc subgroup analysis showed that OS was not significantly different for all subgroups of patients after BuCy compared with TBI-Cy (Fig 3).

Relapse, DFS, and NRM

Sixty and 54 patients relapsed in the BuCy and TBI-Cy groups, respectively, as a result of hematologic relapse in 103 (BuCy, n = 54; TBI-Cy, n = 49) and extramedullary relapse in 22 (BuCy, n = 13; TBI-Cy, n = 9), including CNS relapse in 13 (BuCy, n = 8; TBI-Cy, n = 5). The

TABLE 2. Univariable/Multivariable Analysis in Transplantation

	OS		DFS		Relapse		NRM	
Variable	**Univariate, *P***	**Multivariate, *P* (HR, 95% CI)**	**Univariate, *P***	**Multivariate, *P* (HR, 95% CI)**	**Univariate, *P***	**Multivariate, *P* (HR, 95% CI)**	**Univariate, *P***	**Multivariate, *P* (HR, 95% CI)**
Sex, female *v* male	.802	—	.614	—	.651	—	.815	—
Age, ≥ 35 years *v* < 35 years	.858	.638 (0.912, 0.689 to 1.385)	.577	.782 (1.047, 0.757 to 1.448)	.315	.469 (1.156, 0.781 to 1.712)	.664	.749 (0.910, 0.508 to 1.628)
WBC, ≥ 30 *v* < 30 (10^9/L)	.720	.785 (1.052, 0.730 to 1.517)	.828	.794 (0.958, 0.693 to 1.324)	.822	.949 (0.987, 0.666 to 1.464)	.499	.645 (0.874, 0.491 to 1.553)
Chemotherapy regimen, pediatric-type *v* adult-type	< .001	< .001 (0.457, 0.290 to 0.720)	< .001	< .001 (0.500, 0.344 to 0.727)	< .001	< .001 (0.347, 0.209 to 0.577)	.358	.652 (0.876, 0.493 to 1.556)
Cycles required to achieve CR, ≥ 2 *v* 1	.093	.749 (1.081, 0.671 to 1.743)	.030	.279 (1.253, 0.833 to 1.883)	.031	.706 (1.101, 0.666 to 1.822)	.471	.374 (1.377, 0.680 to 2.786)
MRD status after induction, positive *v* negative	.019	.689 (1.089, 0.716 to 1.657)	.054	.953 (1.011, 0.701 to 1.459)	.016	.802 (1.060, 0.673 to 1.670)	.959	.873 (0.950, 0.508 to 1.777)
MRD status at HSCT, positive *v* negative	< .001	.009 (1.939, 1.179 to 3.188)	< .001	.045 (1.585, 1.009 to 2.489)	< .001	.006 (2.144, 1.238 to 3.714)	.997	.993 (1.004, 0.428 to 2.355)
Donors, MUD *v* MSD	.403	.276 (1.238, 0.843 to 1.816)	.848	.801 (1.045, 0.743 to 1.469)	.385	.345 (0.807, 0.518 to 1.258)	.130	.090 (1.615, 0.929 to 2.810)
aGVHD, II-IV aGVHD *v* 0-I aGVHD	.001	.003 (1.726, 1.207 to 2.468)	.066	.117 (1.292, 0.938 to 1.780)	.071	.028 (0.595, 0.374 to 0.946)	< .001	< .001 (4.117, 2.417 to 7.013)
cGVHD, cGVHD *v* non-cGVHD	< .001	.002 (1.922, 1.273 to 2.900)	.070	.109 (1.399, 0.928 to 2.110)	.226	.122 (0.632, 0.353 to 1.131)	< .001	< .001 (6.184, 3.046 to 12.555)
Conditioning regimens, BuCy *v* TBI-Cy	.507	.896 (0.977, 0.689 to 1.385)	.582	.955 (1.009, 0.746 to 1.364)	.518	.794 (1.051, 0.724 to 1.524)	.963	.840 (0.948, 0.564 to 1.593)

Abbreviations: aGVHD, acute graft-versus-host disease; BuCy, busulfan plus cyclophosphamide; cGVHD, chronic graft-versus-host disease; CR, complete remission; DFS, disease-free survival; HR, hazard ratio; HSCT, hematopoietic stem-cell transplantation; MRD, Minimal residual disease; MSD, matched sibling donors; MUD, matched unrelated donor; NRM, nonrelapse mortality; OS, overall survival; TBI-Cy, total body irradiation plus cyclophosphamide.

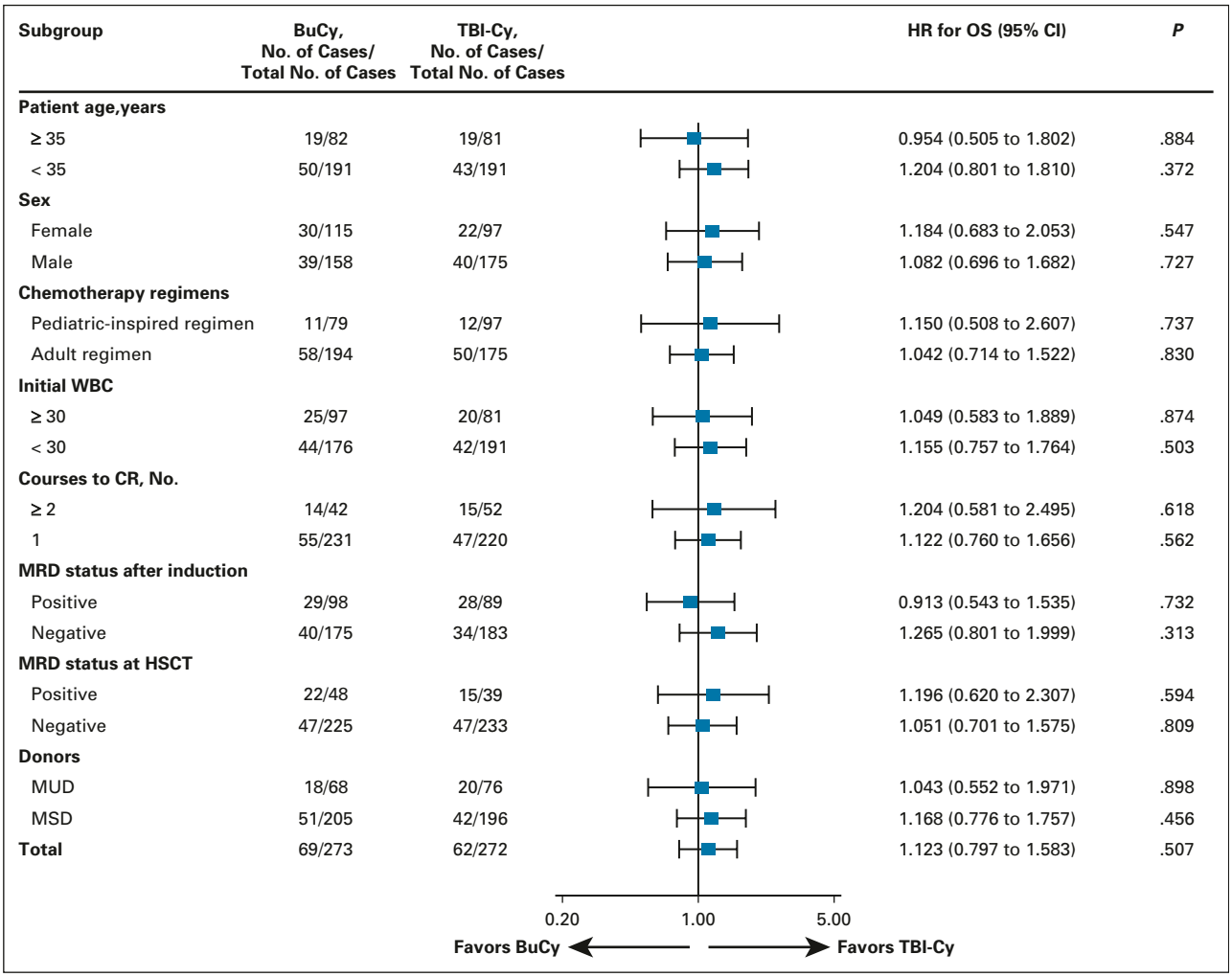

FIG 3. Subgroup analysis of overall survival in patients receiving BuCy or TBI-Cy. BuCy, busulfan plus cyclophosphamide; CR, complete remission; HR, hazard ratio; HSCT, hematopoietic stem-cell transplantation; MRD, minimal residual disease; MSD, matched sibling donor; MUD, matched unrelated donor; OS, overall survival; TBI-Cy, total body irradiation plus cyclophosphamide.

median times of relapse were 8.5 (interquartile range, 5.0-14.4) months and 7.8 (4.2-16.2) months in BuCy and TBI-Cy groups, respectively (P = .697), and the 2-year relapse was 20.2% (95% CI, 15.6 to 25.1) and 18.4% (95% CI, 14.0 to 23.2; P = .616; Fig 2B). Of 114 relapsed patients, six abandoned treatments, 17 received a second transplantation, and others received chemotherapy, donor lymphocyte infusion, or chimeric antigen receptor T-cell immunotherapy. Eventually, 43 patients (BuCy, n = 21; TBI-Cy, n = 22) survived at the last follow-up. In the patients who relapsed post-transplantation, there was no difference in OS between groups (P = .931; Appendix Fig A1 [online only]). The 2-year DFS was 68.9% (95% CI, 63.6 to 74.6) and 70.6% (95% CI, 65.4 to 76.2; P = .643; Fig 2C). The 100-day NRM was 4.8% (95% CI, 1.9 to 6.4) and 3.7% (95% CI, 2.7 to 7.8; P = .527); the 1-year NRM was 9.2% (95% CI, 6.1 to 13.0) and 9.2% (95% CI, 6.1 to 13.0; P = .984), and the 2-year NRM was 11.0% (95% CI, 7.6 to 15.0) and 11.0% (95% CI, 7.7 to 15.1; P = .988; Fig 2D), respectively.

Post hoc multivariable analysis of risk factors for relapse, DFS, and NRM is presented in Table 2. The results showed that pediatric-type chemotherapy and aGVHD were associated with lower relapse. MRD^+ at transplantation had a higher relapse and worse DFS, whereas pediatric-type chemotherapy was associated with better DFS. aGVHD and cGVHD were the risk factors for NRM.

Safety

RRT within 28 days post-transplantation is presented in Appendix Table A4 (online only). The most common RRT was oral mucositis. Grade 3 or worse RRT was reported for 28 (10.3%) of 273 patients after BuCy and 25 (9.2%) of 272 patients after TBI-Cy, and there was no difference between groups (P = .675). Three patients died from RRT in the BuCy group (intracranial hemorrhage = 1, veno-occlusive disease = 1 and hemorrhagic cystitis = 1), whereas no

TABLE 3. Adverse Events

AE	BuCy (n = 273)				TBI-Cy (n = 272)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Cardiac disorders	29 (10.6)	8 (2.9)	0 (0.0)	1 (0.4)	25 (9.2)	11 (4.0)	0 (0.0)	1 (0.7)
GI disorders[a]	123 (45.1)	77 (28.2)	7 (2.6)	0 (0.0)	131 (48.2)	70 (27.6)	5 (1.8)	0 (0.0)
Hepatobiliary/pancreatic disorders[a]	5 (1.8)	2 (0.7)	1 (0.4)	1 (0.4)	2 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)
Immune system disorders	13 (4.8)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.7)	0 (0.0)	0 (0.0)
Infections[b]	43 (15.8)	58 (21.2)	15 (5.5)	6 (2.2)	41 (15.1)	55 (16.5)	18 (6.6)	7 (1.8)
Metabolism and nutrition disorders	39 (14.3)	13 (4.8)	0 (0.0)	0 (0.0)	33 (12.1)	10 (3.6)	0 (0.0)	0 (0.0)
Musculoskeletal/connective tissue	11 (4.0)	2 (0.7)	0 (0.0)	0 (0.0)	15 (5.5)	1 (0.4)	0 (0.0)	0 (0.0)
Neoplasms[c]	—	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	—	1 (0.4)	1 (0.4)
Nervous system disorders	32 (11.7)	3 (1.1)	2 (0.7)	1 (0.4)	29 (10.7)	3 (1.1)	1 (0.4)	0 (0.0)
Renal and urinary disorders	45 (16.5)	15 (5.5)	4 (1.5)	1 (0.4)	37 (13.6)	7 (2.6)	2 (0.7)	0 (0.0)
Respiratory disorders	40 (14.7)	12 (4.4)	2 (0.7)	0 (0.0)	46 (16.9)	18 (6.6)	5 (1.8)	0 (0.0)
Skin and subcutaneous tissue disorders[a]	22 (8.1)	5 (1.8)	0 (0.0)	0 (0.0)	16 (5.9)	3 (1.1)	0 (0.0)	0 (0.0)
Vascular disorders	15 (5.5)	4 (1.5)	1 (0.4)	1 (0.7)	17 (1.5)	3 (0.4)	1 (0.4)	1 (0.4)
General disorders and administration site conditions	75 (27.5)	7 (2.6)	0 (0.0)	0 (0.0)	81 (29.8)	11 (4.0)	0 (0.0)	0 (0.0)
aGVHD	63 (23.1)	56 (20.5)	24 (8.8)	5 (1.8)	67 (24.6)	49 (18.0)	24 (8.8)	4 (1.5)
cGVHD	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)

NOTE. Data are No. of patients (%). Only grade 1-2 AEs that occurred in 10% of patients or more in any group are reported, whereas all grade 3, 4, and 5 AEs are reported.

Abbreviations: AE, adverse event; aGVHD, acute GVHD; BuCy, busulfan plus cyclophosphamide; cGVHD, chronic GVHD; GVHD, graft-versus-host disease;TBI-Cy, total body irradiation plus cyclophosphamide.

[a]Excluded the patients with GVHD.

[b]Excluded the patients with cytomegalovirus viremia and Epstein Barr virus viremia.

[c]Included post-transplant lymphoproliferative diseases.

patient died from RRT in the TBI-Cy group. AEs recorded within 100 days post-transplantation are detailed in Table 3. The most common nonhematologic AEs were GI disorders. Grade 3 or worse nonhematologic AEs were reported in 177 (64.8%) of 273 patients after BuCy and 163 (60.0%) of 272 patients after TBI-Cy, with no difference between the two groups ($P = .237$). AEs within 100 days with an outcome of death were reported in 16 (5.9%) patients after BuCy and 14 (5.1%) patients after TBI-Cy.

The 100-day grade 2-4 aGVHD was 30.8% (95% CI, 25.4 to 36.3) and 27.9% (95% CI, 22.7 to 33.4; $P = .463$, Appendix Fig A2A [online only]), and grade 3-4 aGVHD was 10.6% (95% CI, 7.3 to 14.6) and 10.3% (95% CI, 7.0 to 14.3; $P = .870$, Appendix Fig A2B) in the BuCy and TBI-Cy groups, respectively. Correspondingly, 2-year cGVHD was 31.1% (95% CI, 25.7 to 36.7) and 28.7% (95% CI, 23.4 to 34.1; $P = .524$, Appendix Fig A2C), and severe cGVHD was 7.0% (95% CI, 4.3 to 10.4) and 8.5% (95% CI, 5.5 to 12.2; $P = .538$, Appendix Fig A2D).

Late effects were analyzed in 465 patients who were disease-free at 6 months post-transplantation (BuCy, n = 231 and TBI-Cy, n = 234) and are detailed in Appendix Table A5 (online only). Among these patients, 167 had at least one late effect (84 [36.4%] and 93 [39.7%] for BuCy and TBI-Cy), with no difference between the two groups ($P = .453$).

DISCUSSION

In this RCT, the BuCy regimen has noninferior efficiency and safety to TBI-Cy in patients with adult standard-risk B-ALL in CR1 undergoing allo-HSCT.

It remains controversial whether the BuCy regimen has comparable survival as TBI-Cy in B-ALL. Most studies suggested that intravenous Bu-based regimens led to similar survival in ALL compared with TBI-based regimens.[9,10,26] By contrast, others showed that Bu-based regimens gave worse survival than TBI-based,[11,12] yet a retrospective report suggested that BuCy resulted in better DFS than TBI-Cy.[27] However, these results are mainly derived from retrospective studies. Recently, Peters et al[14] reported an early-terminating RCT in 417 childhood patients with high-risk ALL in complete remission who were randomly assigned to receive TBI or chemotherapy conditioning. The results suggested that TBI plus etoposide might prolong survival, with the 2-year OS of 91% after TBI and 75% after chemotherapy conditioning.

Therefore, the RCT was early terminated.[14] In our study, similar survival and DFS were observed in BuCy and TBI-Cy groups in patients with adult standard-risk B-ALL in CR1. The reasonable interpretations of different results from the two RCTs might be that the two studies focused on different populations and conditionings. Our study enrolled adults and adolescents with standard-risk B-ALL in CR1, whereas Peters' study enrolled a heterogeneous population of children with high-risk ALL in CR1-3, which included B-ALL and T-cell-ALL. The conditionings in our study were BuCy and TBI-Cy, whereas the conditionings in the study by Peters et al were TBI plus etoposide versus chemotherapy conditioning including Bu-based and treosulfan-based regimens. Etoposide was also used in TBI-based regimens. Some studies showed that etoposide plus TBI-based regimens were similar to or better than TBI-Cy.[28,29] It is also worth noting that the most common TBI schedules reported including in Peters' study were performed with a 2 Gy fraction twice a day to a dose of 12 Gy, whereas TBI in our study was delivered with 4.5 Gy/d to a dose of 9 Gy. Some studies reported that high-dose TBI ($\geq$ 12 Gy) resulted in a significant improvement in relapse despite possibly leading to worse NRM,[30-32] whereas in other studies, it gave equivalent OS compared with low-dose TBI regimens ($<$ 12 Gy).[33-36] It cannot be excluded that the present TBI regimen with a total dose of 9 Gy might have been slightly suboptimal for patients with ALL.

It is well known that oral Bu as a conditioning regimen because of its wide variability in bioavailability is associated with higher RRT, such as veno-occlusive disease and thrombotic microangiopathy, resulting in higher NRM than TBI-based regimens.[37,38] Intravenous Bu significantly overcomes variation of bioavailability.[39] Recent studies have confirmed that intravenous Bu reduced RRT compared with oral Bu, making a comparable RRT and NRM with TBI-based regimens.[9,39,40] In our study, there was no significant difference in the RRT or NRM.

Relapse is still the leading cause of failure post-transplantation. Various factors influence leukemia relapse, such as MRD status before transplantation and conditioning. Traditionally, oral Bu-based regimens were associated with higher relapse than TBI-based in ALL.[12,41] In the era of intravenous Bu, it remains controversial whether Bu-based regimens result in noninferior relapse than TBI-based.[9,10,12,13,27,41] Most studies demonstrated that Bu-based regimens result in worse relapse than TBI-based.[10,12,13,41] However, others suggested that Bu-based regimens had comparable relapse with TBI-based,[9,27] which is attributed to stable pharmacokinetic variability and crossing the blood-brain barrier in intravenous Bu.[42] In our study, similar relapse was observed in the two groups, which is consistent with some studies[9,27] but not with others.[10,12,13,41] MRD^+ before transplantation was a risk factor affecting the relapse post-transplantation. In the univariable analysis, MRD^+ after induction and at HSCT was the risk factor for OS and relapse, but multivariable analysis revealed that only MRD^+ at HSCT was associated with poor OS and relapse.

A major concern for patients undergoing allo-HSCT is long-term toxicities resulting in late morbidity and mortality. It has been reported that TBI is associated with an increased risk of late effects.[5,43] However, in our study, we did not find a higher incidence of late effects in the TBI-Cy than BuCy groups, which is contrary to previous reports.[5,43] The reasonable explanation may be that TBI dose in our study was not as high as those in other reports[5,43] and there was an insufficient follow-up period to observe more late effects onset. Furthermore, a low dose rate of $<$ 0.06 Gy/min was used in our study, which might decrease the incidence of late effects such as interstitial pneumonitis and cataracts.

Our study had some limitations. First, a part of patients enrolled were adolescent and young adults in CR1, and whether this population is suitable for allo-HSCT still deserves further discussion. Second, haploidentical donors are the main source in some region.[2,44] Whether Bu-based versus TBI-based regimens have comparable outcomes in patients undergoing haploidentical transplantation is also worthy of validation in further clinical trial.

In conclusion, our study shows that the BuCy regimen results in noninferior OS, relapse, DFS, and NRM compared with TBI-Cy (4.5 Gy $\times$ 2) in patients with adult standard-risk B-ALL in CR1 undergoing HLA-matched allo-HSCT. The BuCy regimen might be an alternative conditioning for these populations undergoing allo-HSCT.

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EQUAL CONTRIBUTION

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Busulfan Plus Cyclophosphamide Versus Total Body Irradiation Plus Cyclophosphamide for Adults Acute B Lymphoblastic Leukemia: An Open-Label, Multicenter, Phase III Trial

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No potential conflicts of interest were reported.

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APPENDIX

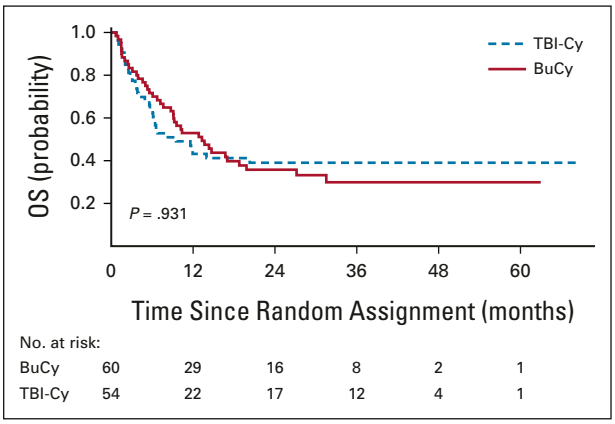

FIG A1. Postrelapse OS according to conditioning regimens. BuCy, busulfan plus cyclophosphamide; OS, overall survival; TBI-Cy, total body irradiation plus cyclophosphamide.

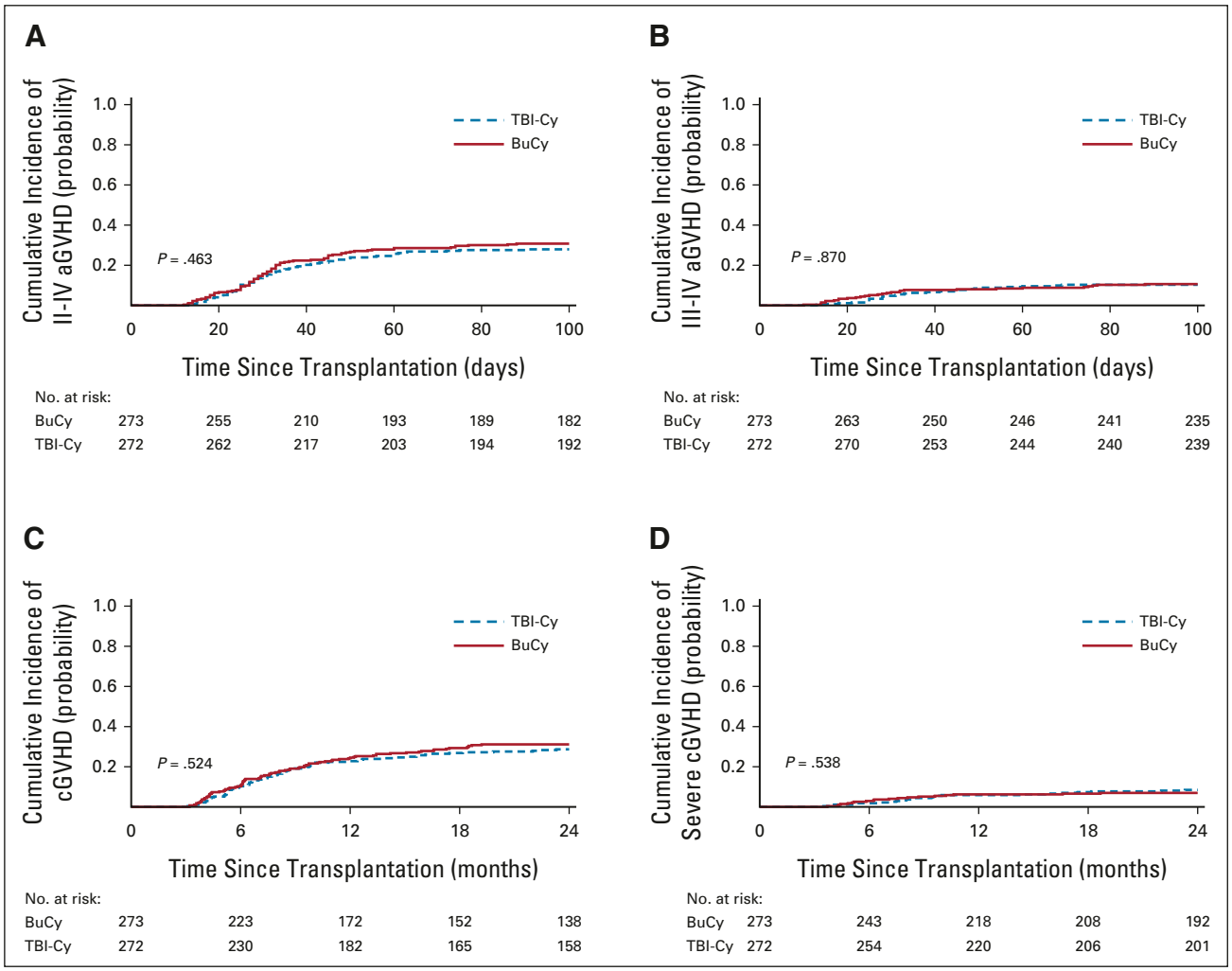

FIG A2. Graft-versus-host disease incidence of allogeneic-hematopoietic stem-cell transplantation with BuCy or TBI-Cy conditioning regimens. Cumulative incidence of (A) II-IV aGVHD, (B) III-IV aGVHD, (C) cGVHD, and (D) severe cGVHD by conditioning regimens. aGVHD, acute graft-versus-host disease; BuCy, busulfan plus cyclophosphamide; cGVHD, chronic graft-versus-host disease; TBI-Cy, total body irradiation plus cyclophosphamide.

TABLE A1. PDT-ALL-2016 Chemotherapy Protocols for Adult B-Cell ALL

Treatment Phase	Dose[a]	Time Administered
Prephase		
Dexamethasone	8 mg/m^2	D1-4
Induction		
VICLD + CAM		
Vincristine (maximum 2 mg)	1.2 mg/m^2	D1, 8, 15, 22
Idarubicin	10 mg/m^2	D1, 8
Cyclophosphamide	1 g/m^2	D1, 8, 25
Peg asparaginase	2,000 IU/m^2	D1, 15[b]
Dexamethasone	0.15 mg/kg	D1-24
Cytarabine	25 mg/m^2	D25-31
6-Mercaptopurine	60 mg/m^2	D25-31
VLCAM[c]		
Vincristine (maximum 2 mg)	1.5 mg/m^2	D46, 53
Peg asparaginase	2,000 IU/m^2	D46
Cyclophosphamide	1 g/m^2	D46
Cytarabine	2 g/m^2	D46, 47
6-Mercaptopurine	60 mg/m^2	D46-52
Consolidation		
Block 1		
Cytarabine	2 g/m^2 once every 12 h	D1-2
Dexamethasone	10 mg/m^2	D1-2
Peg asparaginase	2,000 IU/m^2	D2
6-Mercaptopurine	60 mg/m^2	D1-7
Block 2		
Methotrexate	3 g/m^2	D15
Dexamethasone	10 mg/m^2	D15
Peg asparaginase	2,000 IU/m^2	D16
6-Mercaptopurine	60 mg/m^2	D15-21
Block 3		
Cyclophosphamide	0.5 g/m^2	D29-30
Peg asparaginase	2,000 IU/m^2	D30
Etoposide	75 mg/m^2	D29-30
6-Mercaptopurine	60 mg/m^2	D29-35

Abbreviations: ALL, acute lymphoblastic leukemia; CAM, cyclophosphamide + cytarabine + 6-mercaptopurine; D, day; MRD, minimal residual disease; VICLD, vincristine + idarubicin + cyclophosphamide + peg asparaginase + dexamethasone; VLCAM, vincristine + peg asparaginase + cyclophosphamide + cytarabine + 6-mercaptopurine.

[a]Doses are once daily unless otherwise specified.

[a]If MRD > 1% at day 15.

[b]If MRD > 0.1% at day 30.

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TABLE A2. Adult Chemotherapy Regimen Protocols for Adult B-Cell Acute Lymphoblastic Leukemia

Treatment Phase	Dose[a]	Time Administered
Prephase		
Dexamethasone	8 mg/m^2	D1-4
Induction		
VDLP		
Vincristine (maximum 2 mg)	1.4 mg/m^2	D1, 8, 15, 22
Daunorubicin	45 mg/m2	D1, 8
Peg asparaginase	2,000 IU/m^2	D15
Prednisone	1 mg/kg	D1-28
Consolidation		
Hyper-CVAD A		Courses 1, 3
Dexamethasone	40 mg	D1-4, 11-14
Cyclophosphamide	300 mg/m^2 once every 12 h	D1-3
Vincristine	2 mg	D4, 11
Doxorubicin	50 mg/m^2	D4
Hyper-CVAD B		Courses 2, 4
Methotrexate	1 g/m^2	D1
Cytarabine	3 g/m^2 once every 12 h	D2, 3
Methylprednisolone	50 mg twice a day	D1-3

Abbreviations: CVAD, cyclophosphamide + vincristine + doxorubicin + dexamethasone; D, day; VDLP, vincristine + daunorubicin + peg asparaginase + prednisone.

[a]Doses are once daily unless otherwise specified.

TABLE A3. The Causes of Death

Cause of Death	BuCy, No. (%)	TBI-Cy, No. (%)	Total, No. (%)
Relapse	39 (56.5)	32 (51.6)	71 (54.2)
Infections	10 (14.5)	15 (24.2)	25 (19.1)
aGVHD	6 (8.7)	4 (6.5)	10 (7.6)
cGVHD	4 (5.8)	3 (4.8)	7 (5.3)
Organ failure	4 (5.8)	2 (3.2)	6 (4.6)
Neoplasms	4 (5.8)	3 (4.8)	7 (5.3)
Others	1 (1.4)	2 (3.2)	3 (2.3)
Unknown cause	1 (1.4)	1 (1.6)	2 (1.5)
Total	69	62	131

Abbreviations: aGVHD, acute graft-versus-host disease; BuCy, busulfan plus cyclophosphamide; cGVHD, chronic graft-versus-host disease; TBI-Cy, total body irradiation plus cyclophosphamide.

TABLE A4. Regimen-Related Toxicity According to Bearman's Grading System

	BuCy (n = 273)				TBI-Cy (n = 272)			
Regimen-Related Toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Heart	10 (3.7)	5 (1.8)	2 (0.7)	0 (0.0)	8 (2.9)	6 (2.2)	3 (1.1)	0 (0.0)
Bladder	7 (2.6)	16 (5.9)	5 (1.8)	1 (0.4)	6 (2.2)	5 (1.8)	2 (0.7)	0 (0.0)
Kidney	11 (4.0)	3 (1.1)	0 (0.0)	0 (0.0)	13 (4.8)	4 (1.5)	1 (0.4)	0 (0.0)
Lungs	2 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)	3 (1.1)	6 (2.2)	1 (0.4)	0 (0.0)
Liver	19 (7.0)	13 (4.8)	5 (1.8)	1 (0.4)	16 (5.9)	10 (3.7)	3 (1.1)	0 (0.0)
CNS	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)
Oral mucosa	90 (33.0)	55 (20.1)	12 (4.4)	0 (0.0)	82 (30.1)	51 (18.8)	10 (3.7)	0 (0.0)
Gut	54 (19.8)	10 (3.7)	6 (2.2)	0 (0.0)	61 (22.4)	13 (4.8)	8 (2.9)	0 (0.0)

NOTE. Data are No. of patients (%).

Abbreviations: BuCy, busulfan plus cyclophosphamide; TBI-Cy, total body irradiation plus cyclophosphamide.

TABLE A5. Late Effects

	BuCy (n = 230)				TBI-Cy (n = 232)			
Late Effect	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Late-onset infections	15 (6.5)	7 (3.0)	5 (2.2)	4 (1.7)	17 (7.3)	4 (1.7)	3 (1.3)	7 (3.0)
Oral late effects	9 (3.9)	2 (0.9)	1 (0.4)	0 (0.0)	13 (5.6)	1 (0.4)	1 (0.4)	0 (0.0)
GI late effects	2 (0.9)	3 (1.3)	2 (0.9)	0 (0.0)	1 (0.4)	2 (0.9)	1 (0.4)	0 (0.0)
Musculoskeletal late effects	17 (7.4)	5 (2.2)	1 (0.4)	0 (0.0)	15 (6.5)	4 (1.7)	0 (0.0)	0 (0.0)
Respiratory late effects	12 (5.2)	6 (2.6)	0 (0.0)	0 (0.0)	10 (4.3)	7 (3.0)	1 (0.4)	0 (0.0)
Endocrine late effects	13 (5.7)	3 (1.3)	2 (0.9)	0 (0.0)	11 (4.7)	5 (2.2)	1 (0.4)	0 (0.0)
Ocular late effects	28 (12.2)	4 (1.7)	0 (0.0)	0 (0.0)	33 (14.2)	6 (2.6)	1 (0.4)	0 (0.0)
Neoplasms	—	0 (0.0)	1 (0.4)	2 (0.9)	—	0 (0.0)	1 (0.4)	1 (0.4)
Nervous system late effects	2 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.3)	0 (0.0)	0 (0.0)
Urinary late effects	2 (0.9)	2 (0.9)	1 (0.4)	0 (0.0)	3 (1.3)	1 (0.4)	0 (0.0)	1 (0.4)
Cardiovascular late effects	14 (6.1)	8 (3.5)	3 (1.3)	1 (0.4)	11 (4.7)	7 (3.0)	5 (2.2)	1 (0.4)
Ear-nose-throat late effects	3 (1.3)	1 (0.4)	0 (0.0)	0 (0.0)	5 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)

NOTE. Data are No. of patients (%).

Abbreviations: BuCy, busulfan plus cyclophosphamide; TBI-Cy, total body irradiation plus cyclophosphamide.

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